REMARKS

Claims 1-5, 7-12, and 14-64 are currently pending in the application. Claims 6 and 13 are canceled. Claims 1-5, and 7-12 are amended. Claims 14-64 are newly added. The amendments and newly added claims find support in the specification.

Claim 7, which was previously independent, has now been made to depend on claim 1. Support for this dependency is found on pages 5-7 of the specification . Lines 17-19 of page 5 discloses that the identification of the papilloma virus is a preferred feature of the invention in conjunction with detection. Furthermore on page 6 of the specification beginning at line 26 it is disclosed that the invention may involve determining the type of the papilloma infection in conjunction with its actual detection. Therefore, the features brought together by claim 7 now being dependent on claims 1-5 is supported and described in the specification.

In base Claim 1, the term "*obtaining*" in the recitation of the phrase "obtaining a sample of the organism's cells" has been replaced with the phrase "*contacting in vitro*". Support for this substitution may be found throughout the specification, including Examples 5 and 6.

The preamble of base claim 1, which is directed to a method that comprises a molecule that binds specifically to mucosal papilloma virus E4 protein, has been amended to recite a "method of detecting *a precancerous lesion resulting from a mucosal* papilloma virus". Support for this amendment is found in the specification on page 13, lines 9-12 where it is disclosed "It has surprisingly been found that E4 expression correlates strongly with vegetative DNA replication in HPV-infected cells, making detection of E4 expression a particularly appropriate indicator of HPV infection, and thus particularly useful in screening for precancerous cervical lesions".

Claims 14 to 64 are added to avoid multiple dependent claims. No new matter is added.

Priority

The Office Action states that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 because an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 C.F.R. 1.78).

Applicant has amended the first line of the specification to include the proper priority information. Accordingly, Applicant submits that the application complies with the conditions

necessary for receiving the benefit of the priority applications listed in the first line of the specification.

Claim Objections

The office action states that Claims 8-12 are objected to under 37 C.F.R. 1.75 (C) as being in improper form because a multiple dependent claim can not depend from another multiple dependent claim. Applicant has amended the claims so that no multiple dependent claim is dependent from another multiple dependent claim. Accordingly, Applicant submits withdrawal of the objection to claims 8-12.

Claims Rejection 35 U.S.C. 102

The Office Action states that claims 1-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Palefsky et al. or by Doorbar et al. and directs attention to Table 1 and Figure 2(a) of the Palefsky et al. reference.

Applicant submits that there are at least two reasons why the reference may not be said to anticipate the invention of the instant claims. First, the scientific validity of the Palefsky et al. reference is questionable. Second, even if, for the sake of argument, the Palefsky reference is accepted as scientifically valid, the reference does not teach the same invention as instantly claimed.

Applicants submit that the Palefsky et al. reference was controversial when it was published, since before then the staining of E4 protein in HPV infected cells was thought to be cytoplasmic. This is in contrast to the strictly nuclear staining reported by Palefsky et al. For example, Crum et al. (1990, Virology 178: 238-246) showed cytoplasmic localization of HPV 16 E4. Not only was the Palefsky et al. reference suspect when it was published, subsequent publications have shown more conclusively that E4 is cytoplasmic, rather than nuclear. For example, the Doorbar et al. reference cited by the Examiner (Virology, 1992), and Doorbar et al. (1997, Virology 238: 40-52, published November 1997, after the earliest priority date of this application) clearly show the localization of the E4 protein to the cytoplasm, again in contrast to the conclusions of Palefsky et al. While the exact reason that the antibody of Palefsky et al. showed nuclear staining is not known, it is clear from studies published both before and after those reported by Palefsky et al. that the E4 protein is not nuclear. Applicants submit that the

results of Palefsky et al. have not been reproduced by others, while cytoplasmic staining of E4 has been documented in at least three instances by at least two unrelated investigators, in addition to the demonstrations shown in this application.

Therefore, Applicants submit that reproducible scientific studies indicate that the antigen bound by the antibodies of Palefsky et al. is not HPV E4 protein. Thus, the Palefsky et al. reference does not anticipate the instant methods claims.

Even if the scientific conclusions of Palefsky et al. are assumed, strictly for the sake of argument, to be valid, Applicants submit that the reference still does not teach a method of *detecting a precancerous lesion resulting from a mucosal papilloma virus infection in an organism*, the method comprising the step of contacting in vitro a sample of the organism's cells from the site of potential infection, as required by amended claim 1. Rather, Palefsky et al. teach that tissues *already known to be positive or negative for HPV infection* may be tested for the presence of E4 protein, specifically, HPV 16 E4. The reference does not teach a method of detecting HPV infection based on detection of E4 protein. The Palefsky et al. reference teaches that their antibody preparation recognizes E4 protein in *some* histologically normal tissues positive for HPV 16 (page 2139, column 2, last paragraph, and Table 1). This therefore shows that some tissues infected with HPV 16 are *not* recognized as HPV 16 positive by an assay using their antibody preparation. Applicants submit that this argues against Palefsky et al. teaching or suggesting a method of *detecting a precancerous lesion resulting from a mucosal papilloma virus infection in an organism* using a molecule that specifically binds E4 protein, as instantly claimed.

Applicants submit that the Palefsky et al. reference focuses rather, on characterizing the expression pattern of E4 in hopes of understanding the biological function of E4 in the virus. See, for example, page 2132, column 2, second full paragraph, which states "At this time, little is known about the functional role of early region proteins during the progression of HPV-infected lesions from infection of histologically normal tissue to the development of CIN and SCC. As a first approach to this fundamental question, we sought to characterize the expression of early region proteins at each stage of CIN and in invasive cancer".

Because independent claims 1 is not anticipated by the Palefsky et al. reference, its dependent claims are similarly not anticipated by the reference.

Claims Rejection 35 U.S.C. 102

The Office Action states that claims 1-13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Doorbar et al., and directs attention to Figures 2-4 of the Doorbar et al. reference.

Applicants submit that the Doorbar et al. reference does not teach a method of *detecting a precancerous lesion resulting from a mucosal papilloma virus infection in an organism*, the method comprising the step of contacting in vitro a sample of the organism's cells from the site of potential infection, as required by amended claim 1.

The Examiner refers to figures 2, 3 and 4 of the Doorbar reference as evidence that it anticipates the claimed invention. Applicants submit that Figure 2 shows that monoclonal antibodies to HPV E4 bind to HPV 16 E4 protein expressed in bacteria, Figure 3 shows the results of epitope mapping of the monoclonal antibodies against a panel of synthetic HPV 16 peptides, and Figure 4 shows the localization of E4 protein in a lesion known to be HPV 16 positive.

Applicants submit that neither these figures, nor the reference as a whole, teaches a method of *detecting a precancerous lesion resulting from a mucosal papilloma virus infection in an organism*, the method comprising the step of contacting in vitro a sample of the organism's cells from the site of *potential* infection, as required by amended independent claim 1. In particular, Applicants submit that the reference does not teach a method of detecting a *precancerous lesion* , since it shows detection of E4 expression in a lesion *known* to be HPV 16 positive. The reference also does not teach obtaining a sample from the "site of *potential* infection" as recited in claim 1, since the infection is already known. While this may at first seem to be an inconsequential distinction, the key issue is that prior to the present disclosure, detection of HPV infection based on the detection of E4 protein was not thought to work. The Doorbar reference does not even suggest that the molecules (antibodies) taught that specifically bind to E4 are useful for *detecting a precancerous lesion resulting from a mucosal papilloma*

virus infection in an organism. Rather, the reference actually teaches away from the use of their antibodies for detection, since only 1 of 16 CIN biopsies already known to be HPV 16 positive stained positive for E4 expression with those antibodies (page 355, column 1, second paragraph). Therefore, independent claim 1 is not anticipated by Doorbar et al.

Claims Rejection 35 U.S.C. 102

The Office Action states that claims 1-6, 8 and 12 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. 5,415,995, and directs attention to claim 1, parts (13) and (14).

Claim 1, parts (13) and (14) of U.S. 5,415,995 recite the following:

"A method for indicating the presence of human papilloma virus in a clinical sample which comprises the steps of:
(a) providing an antibody-containing composition, said composition containing antibody immunospecific for an epitope having an amino acid sequence selected from the group consisting of.....
(13) Asp-Gln-Asp-Gln-Ser-Gln-Thr-Pro-Glu-Thr-Pro (SEQ ID NO:13), representing residues 48-58 of E4;
(14) Gly-Ser-Thr-Trp-Pro-Thr-Thr-Pro-Pro-Arg-Pro-Ile-Pro-Lys-Pro (SEQ ID NO:14), representing amino acids 20-34 of E4; .....
(b) contacting said clinical sample with said composition under antibody-antigen complex formation conditions,
(c) detecting the formation of antibody-antigen complex resulting from the contacting of step (b), and
(d) relating the detection of complex of step (c) to the presence in the clinical sample of human papilloma virus.".

Applicant notes that the referenced method for indicating the presence of human papilloma virus in a clinical sample is distinct from the instantly claimed method of detecting *a precancerous lesion resulting from a mucosal papilloma virus infection* in an organism, the method comprising the steps of: obtaining contacting in vitro a sample of the organism's cells from the site of potential infection; contacting the cells with a molecule that binds specifically to mucosal papilloma virus- E4 protein; and monitoring said binding.

Not only does '995 not teach the instantly recited method of detecting a precancerous lesion comprising contacting the cells with a molecule that binds specifically to mucosal

papilloma virus- E4 protein, '995 provides no data using an antibody or any other molecule that binds specifically to mucosal papilloma virus- E4 protein.

Further, even after the time of issuance of '995, the state of the art was unpredictable regarding which if any of the papilloma virus-early proteins bound SSC lesions or bound to CIN lesions at various stages. This unpredictability is disclosed in the instant specification, as follows:

"Thus, for example in Fields Virology (Fields et al, [Eds.] Virology Vol. 2, p2099, 3rd Edn. (1996) Raven Press, New York), an authoritative virology text book, it is stated that "Diagnosis of an HPV type in a tissue requires nucleic acid hybridization studies", and "In contrast, screening for cervical carcinoma by detection of expression of HPV polypeptides has generally been disregarded, being considered unsuitable for a number of reasons, primarily because of the difficulty in obtaining suitable reagents and, more significantly, many HPVs produce very little virus protein in mucosal infections, making detection difficult, uncertain and unreliable. Thus, in Fields Virology (cited above) it is stated that "immunologic detection of viral capsid antigens" is "of limited value". The possibility of immunologic detection of other viral antigens is not even considered. If one were to develop a screening method based on detection of expression of viral proteins, the most likely choice of target would be those proteins which are best-characterised, such as L1 or L2. The function of E4 protein is at present unknown. Its expression pattern in cervical lesions has not been determined conclusively in the prior art so the molecule has not been an obvious choice for selection as a target for detecting HPV infection."

This unpredictability is also evident in the data presented in '995, the data including the binding of cellular lesions by antibodies directed to only protein E6. Table 1 of '995 shows the results of staining CIN lesions of various stages and SSC lesion by antibodies directed to four distinct peptides of the same protein, E6. The results show that even antibodies directed to the same protein bound differentially to CIN lesions of various stages, and further that only three of these four peptides bound to SSC lesions. '995 discloses no basis for these variable results and provides no guidance for which, if any, lesions will antibodies directed to the E4 protein epitopes bind to.

Further, Applicant notes that no data with antibodies or any other molecule that binds E4 on the surface of any cells, including precancerous lesions, is disclosed in '995. In view of this lack of guidance in the disclosure of '995, and in view of the unpredictability of E4 protein

expression in CIN and SSC lesions at the time of issuance of '995 as evidenced by Fields Virology discussed above, Applicant submits that '995 does not teach or suggest the instantly claimed method of detecting *a precancerous lesion resulting from a mucosal papilloma virus infection* in an organism comprising contacting the cells with a molecule that binds specifically to mucosal papilloma virus E4 protein.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

The office action states that Claims 1-13 are rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,346,377.

While not necessarily acquiescing to the rejection, Applicant will file a terminal disclaimer upon the indication of allowable claims.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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